According to still further features in the described preferred embodiments, X_3 is any amino acid residue except a glutamic acid residue, Z is an alanine residue, and/or n is an integer from 1 to 15, preferably from 1 to 10.

In a preferred embodiment of the present invention, the conjugate has the amino acid sequence set forth in SEQ ID NO:16.

According to another aspect of the present invention there is provided a method of inhibiting an activity of GSK-3, which comprises contacting cells expressing GSK-3 with an effective amount of the conjugate described hereinabove.

The activity can be a phosphorylation activity and/or an autophosphorylation activity. Contacting the cells can be effected *in vitro* or *in vivo*.

According to further features in preferred embodiments of the invention described below, the method further comprises contacting the cells with at least one an additional active ingredient that is capable of altering an activity of GSK-3.

The additional active ingredient can be insulin or any active ingredient that is capable of inhibiting an activity of GSK-3, such as, but not limited to, lithium, valproic acid and a lithium ion.

Alternatively, the additional active ingredient can be an active ingredient that is capable of downregulating an expression of GSK-3, such as a polynucleotide, and more preferably a small interfering polynucleotide molecule directed to cause intracellular GSK-3 mRNA degradation.

The small interfering polynucleotide molecule can be selected from the group consisting of an RNAi molecule, an anti-sense molecule, a rybozyme molecule and a DNAzyme molecule.

According to yet another aspect of the present invention there is provided a method of potentiating insulin signaling, which comprises contacting insulin responsive cells, *in vitro* or *in vivo*, with an effective amount of the conjugate of the present invention, described hereinabove.

According to further features in preferred embodiments of the invention described below, the method further comprises contacting the cells contacting the cells with insulin.

According to still another aspect of the present invention there is provided a method of treating a biological condition associated with GSK-3 activity, which

Before explaining at least one embodiment of the invention in detail, it is to be understood that the invention is not limited in its application to the details set forth in the following description or exemplified by the Examples. The invention is capable of other embodiments or of being practiced or carried out in various ways. Also, it is to be understood that the phraseology and terminology employed herein is for the purpose of description and should not be regarded as limiting.

The present invention is based on the concept that relatively short peptides, derived from the recognition motif of GSK-3, may serve as enzyme inhibitors. This concept, in turn, is based on the findings that GSK-3 has a unique recognition motif and therefore short peptides which are designed with reference to this motif are highly specific GSK-3 inhibitors, as is widely taught in WO 01/49709 and in U.S. Patent Application No. 20020147146A1, which are incorporated by reference as if fully set forth herein.

The unique recognition motif of GSK-3, set forth in SEQ ID NO:19, is $SX_1X_2X_3S(p)$, where S is serine or threonine, each of X_1, X_2 and X_3 is any amino acid, and S(p) is phosphorylated serine or phosphorylated threonine. Based on this recognition motif, a set of peptides, which differ one from another in various parameters (e.g., length, phosphorylation, sequence, etc.) have been designed, synthesized and were tested for their activity as either substrates or inhibitors of GSK-3 (see, for example, Table 3 and the accompanying description in the Examples section that follows).

Based on these experiments, a number of features, which would render a peptide an efficient GSK-3 inhibitor, have been determined. For example, it was found that the phosphorylated serine or threonine residue in the motif is necessary for binding. Without this residue, the peptide will neither be a substrate nor an inhibitor. It was further determined that a serine (or threonine) residue upstream of the phosphorylated serine (or threonine) residue separated by three additional residues renders the peptide a GSK-3 substrate, whereas replacement of this serine or threonine residue by any other amino acid, preferably alanine, converts the substrate to a GSK-3 inhibitor. The nature of the three amino acids (denoted as $X_1X_2X_3$ in the sequence above) was also found to affect the inhibition activity of the peptide, as is detailed hereinafter in the Examples section. In one particular, in was found that the presence of glutamic acid as the X_3 residue, which is detected in many GSK-3

substrates, reduces the inhibition activity of the peptide and therefore it is preferable to have any amino acid other than glutamic acid at the X_3 position. It was further found that the number of the additional residues, outside the recognition motif, affect the inhibition potency of the peptide, such that, for example, a total number of between 7 and 50, preferably, between 7 and 20, more preferably between 10 and 13 amino acid residues, is preferable.

Hence, as is further described and exemplified in the Examples section that follows, it was found that polypeptides having the amino acid sequence:

$$[Yn\cdots Y_1]ZX_1X_2X_3S(p)[W_1\cdots Wm]$$

wherein m equals 1 or 2; n is an integer from 1 to 50; S(p) is a phosphorylated serine residue or a phosphorylated threonine residue; Z is any amino acid residue excepting serine residue or threonine residue; and X_1, X_2, X_3, Y_1-Yn and W_1-Wm are each independently any amino acid residue, are highly efficient and specific inhibitors of GSK-3.

It was further found that preferred polypeptides are those having an alanine residue at the Z position, having any amino acid residue excepting glutamic acid as X_3, and/or having between 7 and 20 amino acid residues, preferably between 10 and 13 amino acid residues and more preferably between 10 and 11 amino acid residues, such that n equals 1-15, preferably 1-10.

The efficacy and specificity of these polypeptide inhibitors have been successfully demonstrated so far in *in vitro* tests. However, while aiming at evaluating the efficacy of these inhibitors in *in vivo* tests, it was hypothesized by the present inventor that attaching to the polypeptides described above a hydrophobic moiety would enhance their membrane permeability. While reducing this hypothesis to practice, it was surprisingly found, in both *in vitro* and *in vivo* tests, that a conjugate of the polypeptide inhibitor described above and a fatty acid, as a hydrophobic moiety, attached at the N-terminus of the polypeptide, exerts higher inhibition of GSK-3 activity than a corresponding polypeptide devoid of a hydrophobic moiety.

the present invention can have a stabilizing group at one or both termini. Typical stabilizing groups include amido, acetyl, benzyl, phenyl, tosyl, alkoxycarbonyl, alkyl carbonyl, benzyloxycarbonyl and the like end group modifications. Additional modifications include using a "L" amino acid in place of a "D" amino acid at the termini, cyclization of the peptide inhibitor, and amide rather than amino or carboxy termini to inhibit exopeptidase activity.

The peptides of the present invention may or may not be glycosylated. The peptides are not glycosylated, for example, when produced directly by peptide synthesis techniques or are produced in a prokaryotic cell transformed with a recombinant polynucleotide. Eukaryotically-produced peptide molecules are typically glycosylated.

Non-limiting examples of peptides in accordance with the present invention include those that maintain the sequence of a known GSK-3 substrate except for the substitution of the serine or threonine that is at the fourth position upstream of the phosphorylated serine or threonine (denoted as Z in the amino acid sequence described above). Preferably, Z is alanine. When the known substrate from which the inhibitor is derived is the CREB protein, the minimum size of the peptide is 10 residues, with the additional three residues all being upstream of the Z. Similarly, when the substrate from which the peptide is derived is heat shock factor-1 (HSF-1, the minimum number of residues in the peptide must be greater than seven. In addition, preferred peptides according to the present invention exclude glutamic acid at the X_3 position.

Preferred polypeptides according to the present invention are those having an amino acid sequence as set forth in SEQ ID NO: 5, SEQ ID NO:8 or SEQ ID NO:9.

As used herein the phrase "hydrophobic moiety" refers to any substance or a residue thereof that is characterized by hydrophobicity. As is well accepted in the art, the term "residue" describes a major portion of a substance, which is covalently linked to another substance, herein the polypeptide described hereinabove.

Hence, a hydrophobic moiety according to the present invention is preferably a residue of a hydrophobic substance, and is covalently attached to the polypeptide described hereinabove. However, it would be appreciated that the hydrophobic moieties of the present invention can be attached to the polypeptide via any other

WHAT IS CLAIMED IS:

1. A conjugate comprising:

(a) a polypeptide having the amino acid sequence :

$$[Yn\cdots Y_1]ZX_1X_2X_3S(p)[W_1\cdots Wm]$$

wherein,

m equals 1 or 2;

n is an integer from 1 to 50;

S(p) is a phosphorylated serine residue or a phosphorylated threonine residue;

Z is any amino acid residue excepting serine residue or threonine residue; and

X_1, X_2, X_3, Y_1-Yn and W_1-Wm are each independently any amino acid residue; and

(b) at least one hydrophobic moiety being attached to said polypeptide,

the conjugate being capable of inhibiting an activity of glycogen synthase kinase-3 (GSK-3).

2. The conjugate of claim 1, wherein said at least one hydrophobic moiety is attached to an N-terminus and/or a C-terminus of said polypeptide.

3. The conjugate of claim 1, wherein said at least one hydrophobic moiety is attached to an N-terminus of said polypeptide.

4. The conjugate of claim 1, wherein said at least one hydrophobic moiety comprises a hydrophobic peptide sequence.

5. The conjugate of claim 4, wherein said hydrophobic peptide sequence comprises at least one amino acid residue selected from the group consisting of an alanine residue, a cysteine residue, a glycine residue, an isoleucine residue, a leucine residue, a valine residue, a phenylalanine residue, a tyrosine residue, a methionine residue, a proline residue and a tryptophan residue.

6. The conjugate of claim 1, wherein said at least one hydrophobic moiety comprises a fatty acid.

7. The conjugate of claim 6, wherein said fatty acid is attached to at least one amino acid residue.

8. The conjugate of claim 6, wherein said fatty acid is selected from the group consisting of myristic acid, lauric acid, palmitic acid, stearic acid, oleic acid, linoleic acid and linolenic acid.

9. The conjugate of claim 8, wherein said fatty acid is myristic acid.

10. The conjugate of claim 1, wherein X_3 is any amino acid residue except a glutamic acid residue.

11. The conjugate of claim 1, wherein Z is an alanine residue.

12. The conjugate of claim 1, wherein n is an integer from 1 to 15.

13. The conjugate of claim 12, wherein n is an integer from 1 to 10.

14. The conjugate of claim 1, having the amino acid sequence set forth in SEQ ID NO:16.

15. A pharmaceutical composition comprising, as an active ingredient, the conjugate of claim 1, and a pharmaceutically acceptable carrier.

16. The pharmaceutical composition of claim 15, packaged in a packaging material and identified in print, on or in said packaging material, for use in the treatment of a biological condition associated with GSK-3 activity.

17. The pharmaceutical composition of claim 16, wherein said biological condition is selected from the group consisting of obesity, non-insulin dependent

diabetes mellitus, an insulin-dependent condition, an affective disorder, a neurodegenerative disease or disorder and a psychotic disease or disorder.

18. The pharmaceutical composition of claim 17, wherein said affective disorder is selected from the group consisting of a unipolar disorder and a bipolar disorder.

19. The pharmaceutical composition of claim 18, wherein said unipolar disorder is depression.

20. The pharmaceutical composition of claim 18, wherein said bipolar disorder is manic depression.

21. The pharmaceutical composition of claim 17, wherein said neurodegenerative disorder results from an event selected from the group consisting of cerebral ischemia, stroke, traumatic brain injury and bacterial infection.

22. The pharmaceutical composition of claim 17, wherein said neurodegenerative disorder is a chronic neurodegenerative disorder.

23. The pharmaceutical composition of claim 22, wherein said chronic neurodegenerative disorder results from a disease selected from the group consisting of Alzheimer's disease, Huntington's disease, Parkinson's disease, AIDS associated dementia, amyotrophic lateral sclerosis (AML) and multiple sclerosis.

24. The pharmaceutical composition of claim 15, further comprising at least one additional active ingredient that is capable of altering an activity of GSK-3.

25. The pharmaceutical composition of claim 24, wherein said additional active ingredient is insulin.

26. The pharmaceutical composition of claim 24, wherein said additional active ingredient is capable of inhibiting an activity of GSK-3.

27. The pharmaceutical composition of claim 26, wherein said additional active ingredient is selected from the group consisting of a GSK-3 inhibitor, lithium, valproic acid and a lithium ion.

28. The pharmaceutical composition of claim 24, wherein said additional active ingredient is capable of downregulating an expression of GSK-3.

29. The pharmaceutical composition of claim 28, wherein said additional active ingredient is a polynucleotide.

30. The pharmaceutical composition of claim 29, wherein said polynucleotide is a small interfering polynucleotide molecule directed to cause intracellular GSK-3 mRNA degradation.

31. The pharmaceutical composition of claim 30, wherein said small interfering polynucleotide molecule is selected from the group consisting of an RNAi molecule, an anti-sense molecule, a rybozyme molecule and a DNAzyme molecule.

32. The pharmaceutical composition of claim 15, formulated in a delivery form selected from the group consisting of aerosol, aqueous solution, bolus, capsule, colloid, delayed release, depot, dissolvable powder, drops, emulsion, erodible implant, gel, gel capsule, granules, injectable solution, ingestible solution, inhalable solution, lotion, oil solution, pill, suppository, salve, suspension, sustained release, syrup, tablet, tincture, topical cream, transdermal delivery form.

33. The pharmaceutical composition of claim 15, wherein said at least one hydrophobic moiety is attached to an N-terminus and/or a C-terminus of said polypeptide.

34. The pharmaceutical composition of claim 15, wherein said at least one hydrophobic moiety is attached to an N-terminus of said polypeptide.

35. The pharmaceutical composition of claim 15, wherein said at least one hydrophobic moiety comprises a hydrophobic peptide sequence.

36. The pharmaceutical composition of claim 35, wherein said hydrophobic peptide sequence comprises at least one amino acid residue selected from the group consisting of an alanine residue, a cysteine residue, a glycine residue, an isoleucine residue, a leucine residue, a valine residue, a phenylalanine residue, a tyrosine residue, a methionine residue, a proline residue and a tryptophan residue.

37. The pharmaceutical composition of claim 15, wherein said at least one hydrophobic moiety comprises a fatty acid.

38. The pharmaceutical composition of claim 37, wherein said fatty acid is attached to at least one amino acid residue.

39. The pharmaceutical composition of claim 37, wherein said fatty acid is selected from the group consisting of myristic acid, lauric acid, palmitic acid, stearic acid, oleic acid, linoleic acid and linolenic acid.

40. The pharmaceutical composition of claim 39, wherein said fatty acid is myristic acid.

41. The pharmaceutical composition of claim 15, wherein X_3 is any amino acid residue except a glutamic acid residue.

42. The pharmaceutical composition of claim 15, wherein Z is an alanine residue.

43. The pharmaceutical composition of claim 15, wherein n is an integer from 1 to 15.

44. The pharmaceutical composition of claim 43, wherein n is an integer from 1 to 10.

45. The pharmaceutical composition of claim 15, wherein said conjugate has the amino acid sequence set forth in SEQ ID NO:16.

46. A method of inhibiting an activity of GSK-3, the method comprising contacting cells expressing GSK-3 with an effective amount of the conjugate of claim 1.

47. The method of claim 46, wherein said activity is a phosphorylation activity and/or an autophosphorylation activity.

48. The method of claim 46, wherein said contacting is effected *in vitro*.

49. The method of claim 46, wherein said contacting is effected *in vivo*.

50. The method of claim 46, wherein said at least one hydrophobic moiety is attached to an N-terminus and/or a C-terminus of said polypeptide.

51. The method of claim 46, wherein said at least one hydrophobic moiety is attached to an N-terminus of said polypeptide.

52. The method of claim 46, wherein said at least one hydrophobic moiety comprises a hydrophobic peptide sequence.

53. The method of claim 52, wherein said hydrophobic peptide sequence comprises at least one amino acid residue selected from the group consisting of an alanine residue, a cysteine residue, a glycine residue, an isoleucine residue, a leucine residue, a valine residue, a phenylalanine residue, a tyrosine residue, a methionine residue, a proline residue and a tryptophan residue.

54. The method of claim 46, wherein said at least one hydrophobic moiety comprises a fatty acid.

55. The method of claim 54, wherein said fatty acid is attached to at least one amino acid residue.

56. The method of claim 54, wherein said fatty acid is selected from the group consisting of myristic acid, lauric acid, palmitic acid, stearic acid, oleic acid, linoleic acid and linolenic acid.

57. The method of claim 56, wherein said fatty acid is myristic acid.

58. The method of claim 46, wherein X_3 is any amino acid residue except a glutamic acid residue.

59. The method of claim 46, wherein Z is an alanine residue.

60. The method of claim 46, wherein n is an integer from 1 to 15.

61. The method of claim 60, wherein n is an integer from 1 to 10.

62. The method of claim 46, wherein said conjugate has the amino acid sequence set forth in SEQ ID NO:16.

63. The method of claim 46, further comprising contacting said cells with at least one an additional active ingredient, said additional active ingredient being capable of altering an activity of GSK-3.

64. The method of claim 63, wherein said additional active ingredient is insulin.

65. The method of claim 63, wherein said additional active ingredient is capable of inhibiting an activity of GSK-3.

66. The method of claim 65, wherein said additional active ingredient is selected from the group consisting of a GSK-3 inhibitor, lithium, valproic acid and a lithium ion.

67. The method of claim 63, wherein said additional active ingredient is capable of downregulating an expression of GSK-3.

68. The method of claim 67, wherein said additional active ingredient is a polynucleotide.

69. The method of claim 68, wherein said polynucleotide is a small interfering polynucleotide molecule directed to cause intracellular GSK-3 mRNA degradation.

70. The method of claim 69, wherein said small interfering polynucleotide molecule is selected from the group consisting of an RNAi molecule, an anti-sense molecule, a rybozyme molecule and a DNAzyme molecule.

71. A method of potentiating insulin signaling, the method comprising contacting insulin responsive cells with an effective amount of the conjugate of claim 1.

72. The method of claim 71, further comprising contacting said cells with insulin.

73. The method of claim 71, wherein said contacting is effected *in vitro*.

74. The method of claim 71, wherein said contacting is effected *in vivo*.

75. The method of claim 71, wherein said at least one hydrophobic moiety is attached to an N-terminus and/or a C-terminus of said polypeptide.

76. The method of claim 71, wherein said at least one hydrophobic moiety is attached to an N-terminus of said polypeptide.

77. The method of claim 71, wherein said at least one hydrophobic moiety comprises a hydrophobic peptide sequence.

78. The method of claim 77, wherein said hydrophobic peptide sequence comprises at least one amino acid residue selected from the group consisting of an alanine residue, a cysteine residue, a glycine residue, an isoleucine residue, a leucine residue, a valine residue, a phenylalanine residue, a tyrosine residue, a methionine residue, a proline residue and a tryptophan residue.

79. The method of claim 71, wherein said at least one hydrophobic moiety comprises a fatty acid.

80. The method of claim 79, wherein said fatty acid is attached to at least one amino acid residue.

81. The method of claim 79, wherein said at least one fatty acid is selected from the group consisting of myristic acid, lauric acid, palmitic acid, stearic acid, oleic acid, linoleic acid and linolenic acid.

82. The method of claim 81, wherein said fatty acid is myristic acid.

83. The method of claim 71, wherein X_3 is any amino acid residue except a glutamic acid residue.

84. The method of claim 71, wherein Z is an alanine residue.

85. The method of claim 71, wherein n is an integer from 1 to 15.

86. The method of claim 85, wherein n is an integer from 1 to 10.

87. The method of claim 71, wherein said conjugate has the amino acid sequence set forth in SEQ ID NO:16.

88. A method of treating a biological condition associated with GSK-3 activity, the method comprising administering to a subject in need thereof a therapeutically effective amount of the conjugate of claim 1.

89. The method of claim 88, wherein said biological condition is selected from the group consisting of obesity, non-insulin dependent diabetes mellitus, an insulin-dependent condition, an affective disorder, a neurodegenerative disease or disorder and a psychotic disease or disorder.

90. The method of claim 89, wherein said affective disorder is selected from the group consisting of a unipolar disorder and a bipolar disorder.

91. The method of claim 90, wherein said unipolar disorder is depression.

92. The method of claim 90, wherein said bipolar disorder is manic depression.

93. The method of claim 89, wherein said neurodegenerative disorder results from an event selected from the group consisting of cerebral ischemia, stroke, traumatic brain injury and bacterial infection.

94. The method of claim 89, wherein said neurodegenerative disorder is a chronic neurodegenerative disorder.

95. The method of claim 94, wherein said chronic neurodegenerative disorder results from a disease selected from the group consisting of Alzheimer's disease, Huntington's disease, Parkinson's disease, AIDS associated dementia, amyotrophic lateral sclerosis (AML) and multiple sclerosis.

96. The method of claim 89, wherein said psychotic disorder is schizophrenia.

97. The method of claim 88, further comprising co-administering to said subject at least one additional active ingredient, said at least one additional active ingredient being capable of altering an activity of GSK-3.

98. The method of claim 97, wherein said additional active ingredient is insulin.

99. The method of claim 97, wherein said additional active ingredient is capable of inhibiting an activity of GSK-3.

100. The method of claim 99, wherein said additional active ingredient is selected from the group consisting of a GSK-3 inhibitor, lithium, valproic acid and a lithium ion.

101. The method of claim 97, wherein said additional active ingredient is capable of downregulating an expression of GSK-3.

102. The method of claim 101, wherein said additional active ingredient is a polynucleotide.

103. The method of claim 102, wherein said polynucleotide is a small interfering polynucleotide molecule directed to cause intracellular GSK-3 mRNA degradation.

104. The method of claim 103, wherein said small interfering polynucleotide molecule is selected from the group consisting of an RNAi molecule, an anti-sense molecule, a rybozyme molecule and a DNAzyme molecule.

105. The method of claim 88, wherein said at least one hydrophobic moiety is attached to an N-terminus and/or a C-terminus of said polypeptide.

106. The method of claim 88, wherein said at least one hydrophobic moiety is attached to an N-terminus of said polypeptide.

107. The method of claim 88, wherein said at least one hydrophobic moiety comprises a hydrophobic peptide sequence.

108. The method of claim 107, wherein said hydrophobic peptide sequence comprises at least one amino acid residue selected from the group consisting of an alanine residue, a cysteine residue, a glycine residue, an isoleucine residue, a leucine residue, a valine residue, a phenylalanine residue, a tyrosine residue, a methionine residue, a proline residue and a tryptophan residue.

109. The method of claim 88, wherein said at least one hydrophobic moiety comprises a fatty acid.

110. The method of claim 109, wherein said fatty acid is attached to at least one amino acid residue.

111. The method of claim 109, wherein said fatty acid is selected from the group consisting of myristic acid, lauric acid, palmitic acid, stearic acid, oleic acid, linoleic acid and linolenic acid.

112. The method of claim 111, wherein said fatty acid is myristic acid.

113. The method of claim 88, wherein X_3 is any amino acid residue except a glutamic acid residue.

114. The method of claim 88, wherein Z is an alanine residue.

115. The method of claim 88, wherein n is an integer from 1 to 15.

116. The method of claim 115, wherein n is an integer from 1 to 10.

117. The method of claim 88, wherein said conjugate has the amino acid sequence set forth in SEQ ID NO:16.

118. A method of treating an affective disorder, the method comprising administering to a subject in need thereof a therapeutically effective amount of at least one compound that is capable of specifically inhibiting an activity of GSK-3.

119. The method of claim 118, wherein said affective disorder is selected from the group consisting of a unipolar disorder and bipolar disorder.

120. The method of claim 119, wherein said unipolar disorder is depression.

121. The method of claim 119, wherein said bipolar disorder is manic depression.

122. The method of claim 118, wherein said compound is a polypeptide having the amino acid sequence:

$$[Yn\cdots Y_1]ZX_1X_2X_3S(p)[W_1\cdots Wm]$$

wherein,

m equals 1 or 2;

n is an integer from 1 to 50;

S(p) is a phosphorylated serine residue or a phosphorylated threonine residue;

Z is any amino acid residue excepting serine residue or threonine residue; and

X_1, X_2, X_3, Y_1-Yn and W_1-Wm are each independently any amino acid residue.

123. The method of claim 122, wherein X_3 is any amino acid residue except a glutamic acid residue.

124. The method of claim 122, wherein Z is an alanine residue.

125. The method of claim 122, wherein n is an integer from 1 to 15.

126. The method of claim 125, wherein n is an integer from 1 to 10.

127. The method of claim 122, wherein said polypeptide has an amino acid sequence selected from the group consisting of the amino acid sequences set forth in SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:9 and SEQ ID NO:12.

128. The method of claim 122, wherein said polypeptide further comprises at least one hydrophobic moiety being attached thereto.

129. The method of claim 128, wherein said at least one hydrophobic moiety is attached to an N-terminus and/or a C-terminus of said polypeptide.

130. The method of claim 128, wherein said at least one hydrophobic moiety is attached to an N-terminus of said polypeptide.

131. The method of claim 128, wherein said at least one hydrophobic moiety comprises a hydrophobic peptide sequence.

132. The method of claim 131, wherein said hydrophobic peptide sequence comprises at least one amino acid residue selected from the group consisting of an alanine residue, a cysteine residue, a glycine residue, an isoleucine residue, a leucine residue, a valine residue, a phenylalanine residue, a tyrosine residue, a methionine residue, a proline residue and a tryptophan residue.

133. The method of claim 128, wherein said at least one hydrophobic moiety comprises a fatty acid.

134. The method of claim 133, wherein said fatty acid is attached to at least one amino acid residue.

135. The method of claim 133, wherein said fatty acid is selected from the group consisting of myristic acid, lauric acid, palmitic acid, stearic acid, oleic acid, linoleic acid and linolenic acid.

136. The method of claim 135, wherein said fatty acid is myristic acid.

137. The method of claim 128, wherein X_3 is any amino acid residue except a glutamic acid residue.

138. The method of claim 128, wherein Z is an alanine residue.

139. The method of claim 128, wherein n is an integer from 1 to 15.

140. The method of claim 139, wherein n is an integer from 1 to 10.

141. The method of claim 128, wherein said compound has the amino acid sequence set forth in SEQ ID NO:16.

142. A method of up-regulating a β-catenin level in a hippocampus of a subject, the method comprising administering to the subject an effective amount of at least one compound that is capable of specifically inhibiting an activity of GSK-3.

143. The method of claim 142, wherein said compound is a polypeptide having the amino acid sequence:

$$[Yn\cdots Y_1]ZX_1X_2X_3S(p)[W_1\cdots Wm]$$

wherein,

m equals 1 or 2;

n is an integer from 1 to 50;

S(p) is a phosphorylated serine residue or a phosphorylated threonine residue;

Z is any amino acid residue excepting serine residue or threonine residue; and

X_1, X_2, X_3, Y_1-Yn and W_1-Wm are each independently any amino acid residue.

144. The method of claim 143, wherein X_3 is any amino acid residue except A glutamic acid residue.

145. The method of claim 143, wherein Z is an alanine residue.

146. The method of claim 143, wherein n is an integer from 1 to 15.

147. The method of claim 146, wherein n is an integer from 1 to 10.

148. The method of claim 143, wherein said polypeptide has an amino acid sequence selected from the group consisting of the amino acid sequences set forth in SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:9 and SEQ ID NO:12.

149. The method of claim 143, wherein said polypeptide further comprises at least one hydrophobic moiety being attached thereto.

150. The method of claim 149, wherein said at least one hydrophobic moiety is attached to an N-terminus and/or a C-terminus of said polypeptide.

151. The method of claim 149, wherein said at least one hydrophobic moiety is attached to an N-terminus of said polypeptide.

152. The method of claim 149, wherein said at least one hydrophobic moiety comprises a hydrophobic peptide sequence.

153. The method of claim 152, wherein said hydrophobic peptide sequence comprises at least one amino acid residue selected from the group consisting of an alanine residue, a cysteine residue, a glycine residue, an isoleucine residue, a leucine residue, a valine residue, a phenylalanine residue, a tyrosine residue, a methionine residue, a proline residue and a tryptophan residue.

154. The method of claim 149, wherein said at least one hydrophobic moiety comprises a fatty acid.

155. The method of claim 154, wherein said fatty acid is attached to at least one amino acid residue.

156. The method of claim 154, wherein said fatty acid is selected from the group consisting of myristic acid, lauric acid, palmitic acid, stearic acid, oleic acid, linoleic acid and linolenic acid.

157. The method of claim 156, wherein said fatty acid is myristic acid.

158. The method of claim 149, wherein X_3 is any amino acid residue except a glutamic acid residue.

159. The method of claim 149, wherein Z is an alanine residue.

160. The method of claim 149, wherein n is an integer from 1 to 15.

161. The method of claim 160, wherein n is an integer from 1 to 10.

162. The method of claim 149, wherein said compound has the amino acid sequence set forth in SEQ ID NO:16.

163. A process of producing the conjugate of claim 1, the process comprising:

providing said polypeptide;

providing said at least one hydrophobic moiety; and

conjugating said at least one hydrophobic moiety and said polypeptide.

164. The process of claim 163, wherein said providing of said polypeptide is by chemically synthesizing said polypeptide.

165. The process of claim 163, wherein said providing of said polypeptide is by recombinantly producing said polypeptide.

166. The process of claim 163, wherein said conjugate has the amino acid sequence set forth in SEQ ID NO:16.